(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

06 JUL 2004

(43) International Publication Date
12 February 2004 (12.02.2004)

PCT

(10) International Publication Number
WO 2004/013105 A1

(51) International Patent Classification[7]: C07D 223/16, A61K 31/55

(21) International Application Number: PCT/EP2003/007771

(22) International Filing Date: 17 July 2003 (17.07.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
02405653.3 26 July 2002 (26.07.2002) EP

(71) Applicant *(for all designated States except US)*: **CIBA SPECIALTY CHEMICALS HOLGING INC.** [CH/CH]; Klybeckstrasse 11, CH-4057 Basel (CH).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **VAN DER SCHAAF, Paul, Adriaan** [NL/CH]; Marsstrasse 17, CH-4123 Allschwil (CH). **MARCOLLI, Claudia** [CH/CH]; Heinrichstrasse 210, CH-8005 Zürich (CH). **BLATTER, Fritz** [CH/CH]; Oerinstrasse 67, CH-4153 Reinach (CH). **SZELAGIEWICZ, Martin** [CH/CH]; Christoph-Merian-Strasse 1, CH-4142 Münchenstein (CH).

(74) Common Representative: **CIBA SPECIALTY CHEMICALS HOLGING INC.**; Klybeckstrasse 141, CH-4057 Basel (CH).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: CRYSTALLINE POLYMORPHIC AND AMORPHOUS FORMS OF BENAZEPRIL HYDROCHLORIDE

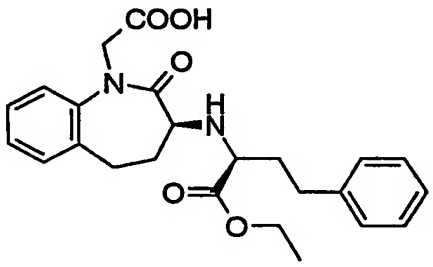
(57) Abstract: The present invention is directed to the polymorphic Form B and the amorphous form of Benazepril hydrochloride. The present invention is also directed to processes for the preparation of Form B and the amorphous form of Benazepril hydrochloride, as well as novel processes for the preparation of Form A. Furthermore, the present invention is directed to pharmaceutical compositions comprising these crystalline forms.

WO 2004/013105 A1

CRISTALLINE POLYMORPHIC AND AMORPHOUS FORMS OF BENAZEPRIL HYDROCHLORIDE

The present invention is directed to a new crystalline form of Benazepril hydrochloride, an amorphous form of Benazepril hydrochloride, processes for the preparation thereof and pharmaceutical compositions comprising these forms.

The present invention relates to a new crystalline form of Benazepril hydrochloride. Benazepril hydrochloride is known by the chemical name: 3-[[(1S)-1-(ethoxy-carbonyl)-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepine-1-acetic acid monohydrochloride. Benazepril has the following formula:



Benazepril is an orally-active ACE-inhibitor, marketed as an antihypertensive. Processes for the preparation of enantiomeric pure Benazepril hydrochloride are described in EP-A-072 352 and US-A-4 575 503 and in the publications by J.W.H. Watthey et al. in J. Med. Chem. (1985), vol. 28, pages 1511-1516, and S.K. Boyer et al. in Helvetica Chimica Acta (1988), vol. 71, pages 337-342.

The processes described in the publications mentioned above result in the isolation of Benazepril hydrochloride in one defined crystalline form, herein designated as Form A. However, it is known that pharmaceutical substances can exhibit polymorphism. Polymorphism is commonly defined as the ability of any substance to have two or more different crystal structures. Drug substances may also encapsulate solvent molecules when crystallized. These solvates or hydrates are referred to as pseudopolymorphs. It is also possible that the amorphous form is encountered. Different polymorphs, pseudopolymorphs or the amorphous form differ in their physical properties such as melting point, solubility etc. These can appreciably influence pharmaceutical properties such as dissolution rate and

bioavailability. It is also economically desirable that the product is stable for extended periods of time without the need for specialised storage conditions. It is therefore important to evaluate polymorphism of drug substances. We now have surprisingly found a novel crystalline form of Benazepril hydrochloride, herein designated as form B, with improved stability as well as the amorphous form of Benazepril hydrochloride.

Accordingly, the present invention is directed to the polymorphic Form B, the amorphous form of Benazepril hydrochloride, processes for the preparation of Form B and the amorphous form of Benazepril hydrochloride, as well as novel processes for the preparation of Form A.

One object of the present invention is a crystalline polymorph of 3-[[(1S)-1-(ethoxy-carbonyl)-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepine-1-acetic acid monohydrochloride which exhibits a characteristic X-ray powder diffraction pattern with characteristic peaks expressed in d-values (Å) at
13.2 (vs), 10.7 (s), 8.8 (m), 6.4 (m), 5.87 (s), 5.75 (m), 5.35 (m), 5.26 (m), 4.87 (m), 4.66 (s), 4.40 (m), 3.86 (m), 3.79 (m), 3.66 (m), 3.60 (m), 3.57 (m), 3.52 (m), 3.45 (m), 3.40 (m), 3.36 (m), 3.27 (m), 3.18 (m), 2.95 (m), 2.72 (m), 2.65 (m);
herein designated as Form B. Here and in the following the abbreviations in brackets mean: (vs) = very strong intensity; (s) = strong intensity; (m) = medium intensity; (w) = weak intensity; and (vw) = very weak intensity.

Small changes in the experimental details can cause small deviation in the d-values of characteristic peaks in the X-ray powder diffraction patterns, see Figures 2 and 3 which are X-ray powder diffraction patterns for Form B.

A discussion of the theory of X-ray powder diffraction patterns can be found in "X-ray diffraction procedures" by H.P. Klug and L.E. Alexander, J. Wiley, New York (1974).

Furthermore, the present invention is directed to processes for the preparation of Form B of Benazepril hydrochloride.

Form B can generally be prepared by addition of an aqueous solution of hydrochloride (HCl) to a solution of the free base of Benazepril in an organic solvent. Examples of such organic

solvents are ketones, for example acetone or methyl ethyl ketone; acetates, for example ethylacetate or isopropylacetate; nitriles, for example acetonitrile; alcohols, for example isopropylalcohol; or ethers, for example methyl-tert.butyl ether or THF.
Preferred as organic solvents are C_3-C_{10}ketones, C_3-C_{10}acetates, C_2-C_{10}nitriles, C_1-C_{10}alcohols or C_2-C_{10}ethers, especially C_3-C_{10}ketones, C_3-C_{10}acetates or C_2-C_{10}ethers. Highly preferred is ethyl acetate. The weight ratio of the organic solvent to the aqueous solution of HCl is preferably 1:1 to 500:1, especially 1:1 to 100:1. Highly preferred is a weight ratio of 5:1 to 100:1. The process can, for example, be carried out at temperatures of from 10 to 60°C. Preferably, the process is carried out at ambient temperature. If desired, during the preparation process seeding with Form B can be carried out. Form B can be isolated by filtration and dried in air or in vacuum.

Form B can also be prepared by stirring a suspension of Form A or the amorphous form of Benazepril hydrochloride in an organic solvent. Examples of such organic solvents are ketones, acetates, nitriles, alcohols or ethers. For these organic solvents the preferences given above apply. Highly preferred are tert-butyl methyl ether, acetone, tetrahydrofuran. The process can, for example, be carried out at temperatures of from 10 to 60°C. Form B can be isolated by filtration and dried in air or in vacuum. It is preferred that the organic solvent contains small amounts of water. The amount of water is preferably about 0.1 to 15%, most preferably about 0.5 to 10%, especially about 1 to 5% by volume of the suspension. If desired, during the preparation process seeding with Form B can be carried out.

Form B can also be prepared by stirring a suspension of Form A or the amorphous form in water. Form B can be isolated by filtration and dried in air or in vacuum. If desired, during the preparation process seeding with Form B can be carried out.

Another object of the present invention are the amorphous form of Benazepril hydrochloride and processes for the preparation thereof.

The amorphous form of Benazepril hydrochloride is characterised by a powder X-ray diffraction pattern substantially as depicted in Figure 4.

The amorphous form of Benazepril hydrochloride can generally be prepared by evaporation of a solution of Benazepril hydrochloride in an organic solvent or water. Preferably by evaporation of a solution of Benazepril hydrochloride in one of the above organic solvents, especially in a C_2-C_{10}ketone, like acetone. According to another preferred embodiment evaporation of a solution of Benazepril hydrochloride in water is carried out. The evaporation is preferably carried out in vacuum at ambient temperature. It is also possible, to carry out evaporation at elevated temperatures.

Furthermore, the present invention is directed to processes for the preparation of Form A of Benazepril hydrochloride.

Form A can generally be prepared by mixing of a solution of Benazepril hydrochloride (preferably a concentrated solution of Benazepril hydrochloride) in an organic solvent, like C_1-C_{10}alcohols, N-methylpyrrolidone (NMP) or N,N-dimethylformamide (DMF), with a non-solvent like alkanes or acetates, especially C_4-C_{12}alkanes or C_1-C_{10}acetates, especially hexane or ethyl acetate. Preferred organic solvents are C_1-C_4alcohols, like methanol and preferably ethanol. It is preferred to add an alcoholic solution of Benazepril hydrochloride to the non-solvent, especially to heptane or ethyl acetate. If desired, during the preparation process seeding with Form A can be carried out.
Form A is preferably prepared in a waterfree medium.

Another object of the present invention are pharmaceutical compositions comprising an effective amount of crystalline polymorphic B, or the amorphous form, and a pharmaceutically acceptable carrier.

The polymorphic Form B may be used as single component or as mixtures with Form A or the amorphous form.

As to the novel polymorphic form of Benazepril hydrochloride it is preferred that these contain 25-100% by weight, especially 50-100% by weight of the novel form, based on the total amount of Benazepril hydrochloride. Preferably, such an amount of the novel polymorphic form of Benazepril hydrochloride is 75-100% by weight, especially 90-100% by weight. Highly preferred is an amount of 95-100% by weight.

The compositions of the invention include powders, granulates, aggregates and other solid compositions comprising crystalline polymorphic B or the amorphous form. In addition, the compositions that are contemplated by the present invention may further include diluents, such as cellulose-derived materials like powdered cellulose, microcrystalline cellulose, microfine cellulose, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, carboxymethyl, cellulose salts and other substituted and unsubstituted celluloses; starch; pregelatinized starch; inorganic diluents like calcium carbonate and calcium diphosphate and other diluents known to the pharmaceutical industry. Yet other suitable diluents include waxes, sugars and sugar alcohols like mannitol and sorbitol, acrylate polymers and copolymers, as well as pectin, dextrin and gelatin.

Further excipients that are within the contemplation of the present invention include binders, such as acacia gum, pregelatinized starch, sodium alginate, glucose and other binders used in wet and dry granulation and direct compression tableting processes. Excipients that also may be present in the solid compositions further include disintegrants like sodium starch glycolate, crospovidone, low-substituted hydroxypropyl cellulose and others. In addition, excipients may include tableting lubricants like magnesium and calcium stearate and sodium stearyl fumarate; flavorings; sweeteners; preservatives; pharmaceutically acceptable dyes and glidants such as silicon dioxide.

The dosages include dosages suitable for oral, buccal, rectal, parenteral (including subcutaneous, intramuscular, and intravenous), inhalant and ophthalmic administration. Although the most suitable route in any given case will depend on the nature and severity of the condition being treated, the most preferred route of the present invention is oral. The dosages may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

Dosage forms include solid dosage forms, like tablets, powders, capsules, suppositories, sachets, troches and losenges as well as liquid suspensions and elixirs. While the description is not intended to be limiting, the invention is also not intended to pertain to true solutions of Benazepril hydrochloride whereupon the properties that distinguish the solid forms of Benazepril hydrochloride are lost. However, the use of the novel forms to prepare such solutions is considered to be within the contemplation of the invention.

Capsule dosages, of course, will contain the solid composition within a capsule which may be made of gelatin or other conventional encapsulating material. Tablets and powders may be coated. Tablets and powders may be coated with an enteric coating. The enteric coated powder forms may have coatings comprising phthalic acid cellulose acetate, hydroxypropylmethyl-cellulose phthalate, polyvinyl alcohol phthalate, carboxymethylethylcellulose, a copolymer of styrene and maleic acid, a copolymer of methacrylic acid and methyl methacrylate, and like materials, and if desired, they may be employed with suitable plasticizers and/or extending agents. A coated tablet may have a coating on the surface of the tablet or may be a tablet comprising a powder or granules with an enteric-coating.

Preferred unit dosages of the pharmaceutical compositions of this invention typically contain from 0.5 to 100 mg of the novel Benazepril hydrochloride forms or mixtures thereof with each other or other forms of Benazepril hydrochloride. More usually, the combined weight of the Benazepril hydrochloride forms of a unit dosage are from 2.5 mg to 80 mg, for example 5, 10, 20 or 40 mg.

The following Examples illustrate the invention in more detail. Temperatures are given in degrees Celsius.

Example 1: Preparation of polymorphic Form B

100 mg of Benazepril hydrochloride Form A was suspended in a mixture of 2 ml tert-butyl methyl ether and 0.1 ml water. This suspension was stirred for 14 hours at 20°C. 78 mg of Benazepril hydrochloride Form B was obtained after filtration and dried in vacuum at 30°C. The obtained Form B was characterized by X-ray powder diffraction, see Fig 2.

Example 2: Preparation of polymorphic Form B

161 mg Benazepril hydrochloride Form A was suspended in 3 ml acetone and stirred for 20 hours at 20°C. This suspension was filtered and dried in air at 30°C. X-ray powder diffraction showed the product to be polymorphic Form B, see Fig 3.

Example 3: Preparation of polymorphic Form B

160 mg Benazepril hydrochloride Form A was suspended in 2 ml THF. This suspension was stirred at ambient temperatures for 5 hours. This suspension was filtered and dried in air at 30°C. X-ray powder diffraction showed the product to be polymorphic Form B.

Example 4: Preparation of polymorphic Form B

86 mg Benazepril free base was dissolved in 3 ml ethyl acetate. Then 0.1 ml of an aqueous 2 molar solution of HCl was added. After adding an additional 3 ml of ethyl acetate and stirring for 3 hours, the product was obtained by filtration and dried in air at ambient temperature. X-ray powder diffraction showed the product to be polymorphic Form B.

Example 5: Preparation of polymorphic Form A

Reference example: 2.4 gram Benazepril free base was dissolved in 60 ml diethyl ether. This solution was stirred for 20 minutes under a gentle stream of HCl gas. The white suspension was stirred for an aditional 15 minutes and then filtered. The white solid was dried in vacuum at 40°C (35 mbar). The product (2.3 gram) was characterized by X-ray powder diffraction, see Fig 1.

Example 6: Preparation of polymorphic Form A

111 mg Benazepril hydrochloride was dissolved in 0.8 ml water-free ethanol. This solution was rapidly added to 10 ml heptane at 20°C. While stirring, the suspension was slowly cooled to 5°C. Then the white precipitate was filtered and dried in vacuum.
X-ray powder diffraction showed the product to be polymorphic Form A.

Example 7: Preparation of the amorphous form

100 mg Benazepril hydrochloride was dissolved in 2 ml water. The solution was filtered and the obtained clear solution was evaporated to dryness at 50°C in vacuum (300 mbar). The obtained white powder was characterized by DSC (Tg = 76°C) and X-ray powder diffraction, see Fig 4.

Brief description of the drawings

Figure 1 is a characteristic X-ray powder diffraction pattern for Form A.
Figure 2 is a characteristic X-ray powder diffraction pattern for Form B.

Figure 3 is another characteristic X-ray powder diffraction pattern for Form B.

Figure 4 is a characteristic X-ray powder diffraction pattern for the amorphous form.

Claims

1. A crystalline polymorph B of 3-[[(1S)-1-(ethoxy-carbonyl)-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepine-1-acetic acid monohydrochloride which exhibits a characteristic X-ray powder diffraction pattern with characteristic peaks expressed in d-values (Å) at 13.2 (vs), 10.7 (s), 8.8 (m), 6.4 (m), 5.87 (s), 5.75 (m), 5.35 (m), 5.26 (m), 4.87 (m), 4.66 (s), 4.40 (m), 3.86 (m), 3.79 (m), 3.66 (m), 3.60 (m), 3.57 (m), 3.52 (m), 3.45 (m), 3.40 (m), 3.36 (m), 3.27 (m), 3.18 (m), 2.95 (m), 2.72 (m), 2.65 (m); wherein (vs) = very strong intensity; (s) = strong intensity; (m) = medium intensity.

2. A crystalline polymorph B of 3-[[(1S)-1-(ethoxy-carbonyl)-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepine-1-acetic acid monohydrochloride having an X-ray powder diffraction pattern substantially as depicted in figure 2.

3. A crystalline polymorph B of 3-[[(1S)-1-(ethoxy-carbonyl)-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepine-1-acetic acid monohydrochloride having an X-ray powder diffraction pattern substantially as depicted in figure 3.

4. An amorphous form of 3-[[(1S)-1-(ethoxy-carbonyl)-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepine-1-acetic acid monohydrochloride.

5. An amorphous form of 3-[[(1S)-1-(ethoxy-carbonyl)-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepine-1-acetic acid monohydrochloride having a powder X-ray diffraction pattern substantially as depicted in Figure 4.

6. A process for the preparation of a crystalline polymorph according to claim 1, wherein an aqueous solution of hydrochloride is added to a solution of the free base 3-[[(1S)-1-(ethoxy-carbonyl)-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepine-1-acetic acid monohydrochloride in an organic solvent.

7. A process according to claim 6, wherein the organic solvent is a C_3-C_{10}ketone, C_3-C_{10}acetate, C_2-C_{10}nitrile, C_1-C_{10}alcohol or C_2-C_{10}ether, or mixtures thereof.

8. A process for the preparation of a crystalline polymorph according to claim 1, wherein a suspension of Form A or the amorphous form 3-[[(1S)-1-(ethoxy-carbonyl)-3-phenyl-propyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepine-1-acetic acid monohydro-chloride is stirred in an organic solvent.

9. A process according to claim 8, wherein the organic solvent is a C_3-C_{10}ketone, C_3-C_{10}acetate, C_2-C_{10}nitrile, C_1-C_{10}alcohol or C_2-C_{10}ether, or mixtures thereof.

10. A process according to claim 8 or 9, wherein the organic solvent is selected from acetone, 1-butanol, 2-butanol, butyl actetate, tert- butylmethyl ether, cumene, dimetylsulfoxide, ethanol, ethylether, ethylformiate, heptane isobutylacetate, isopropyl acetate, methylacetate 3-methyl-1-butanol, methylethyl ketone.

11. A process according to claim 8 or 9, wherein the organic solvent is selected from acetone, methyl ethyl ketone; ethylacetate, isopropylacetate, acetonitrile, isopropylalcohol, methyl-tert.butyl ether and THF.

12. A process according to any of claims 8 to 11, wherein the organic solvent contains small amounts of water.

13. A process according to claim 12, wherein the amount of water is 0.1 to 15% by volume of the suspension of 3-[[(1S)-1-(ethoxy-carbonyl)-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepine-1-acetic acid monohydrochloride.

14. A process according to claim 13, wherein the amount of water is 0.5 to 10% by volume of the suspension of 3-[[(1S)-1-(ethoxy-carbonyl)-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepine-1-acetic acid monohydrochloride.

15. A process for the preparation of a crystalline polymorph according to claim 1 wherein a suspension of Form A or the amorphous form of 3-[[(1S)-1-(ethoxy-carbonyl)-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepine-1-acetic acid monohydrochloride is stirred in water.

16. A process according to any of claims 6 to 15, wherein 3-[[(1S)-1-(ethoxy-carbonyl)-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepine-1-acetic acid monohydrochloride is isolated by filtration and dried in air or vacuum.

17. A process according to any of claims 6 to 16, wherein seeding is carried out with crystals of the crystalline polymorph according to claim 1.

18. A process for the preparation of the amorphous form according claim 4 or 5, wherein a solution 3-[[(1S)-1-(ethoxy-carbonyl)-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepine-1-acetic acid monohydrochloride in an organic solvent or in water is evaporated to dryness.

19. A process according to claim 18, wherein the organic solvent is a C_3-C_{10}ketone.

20. A process according to claim 18 or 19, wherein the organic solvent is acetone.

21. A process for the preparation of crystalline polymorph Form A of 3-[[(1S)-1-(ethoxy-carbonyl)-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepine-1-acetic acid monohydrochloride, wherein a concentrated solution of 3-[[(1S)-1-(ethoxy-carbonyl)-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepine-1-acetic acid monohydrochloride in an organic solvent is mixed with a non-solvent.

22. A process according to claim 21, wherein the organic solvent is an C_1-C_{10}alcohol, tetrahydrofuran, N-methylpyrrolidone or N,N-dimethylformamide and the non-solvent is a C_4-C_{12}alkane or C_1-C_{10}acetate.

23. A process according to claim 21 or 22, wherein a solution of 3-[[(1S)-1-(ethoxy-carbonyl)-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepine-1-acetic acid monohydrochloride in a C_1-C_4alcohol is mixed with heptane.

24. A process according to any of claims 21 to 23, wherein seeding with crystals of the Form A of 3-[[(1S)-1-(ethoxy-carbonyl)-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepine-1-acetic acid monohydrochloride is carried out.

25. A pharmaceutical composition comprising an effective amount of a crystalline polymorphic form according to one of claims 1 to 3 or the amorphous form according to claims 4 or 5, and a pharmaceutically acceptable carrier.

Fig. 1

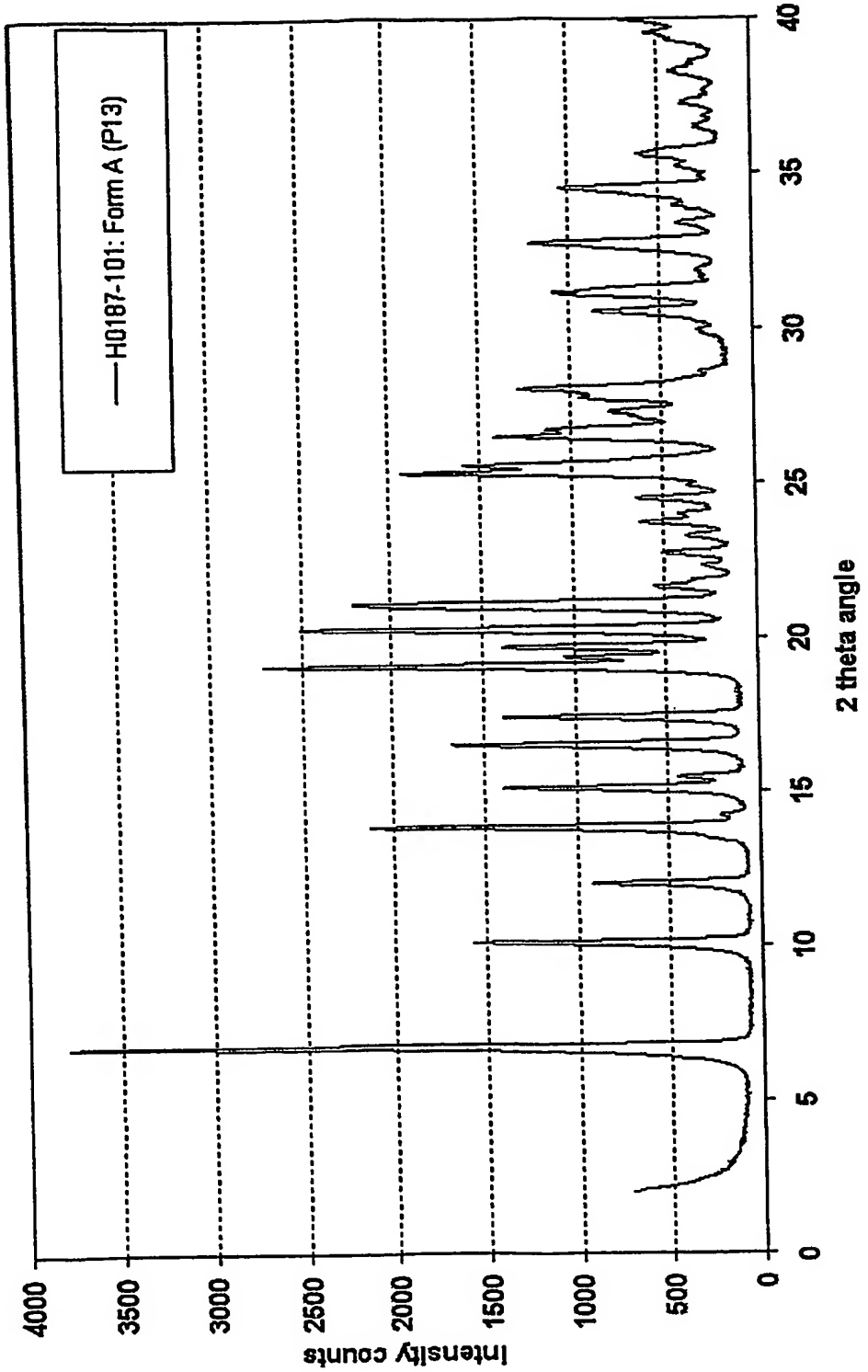

H0187-101: Form A (P13)
Intensity counts
4000
3500
3000
2500
2000
1500
1000
500
0
0
5
10
15
20
25
30
35
40
2 theta angle

Fig. 2

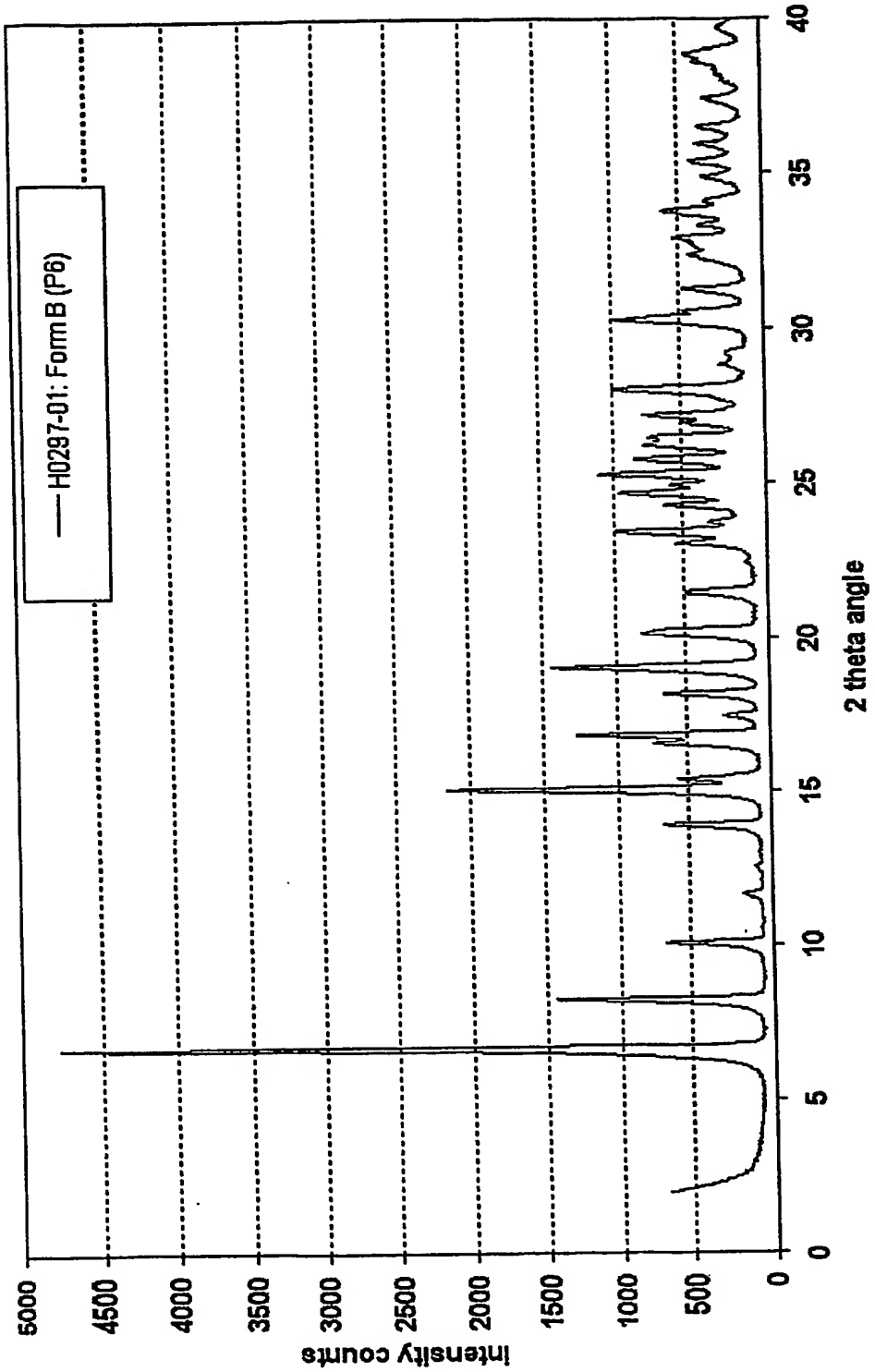

H0297-01: Form B (P6)
Intensity counts
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
0
5
10
15
20
25
30
35
40
2 theta angle

Fig. 3

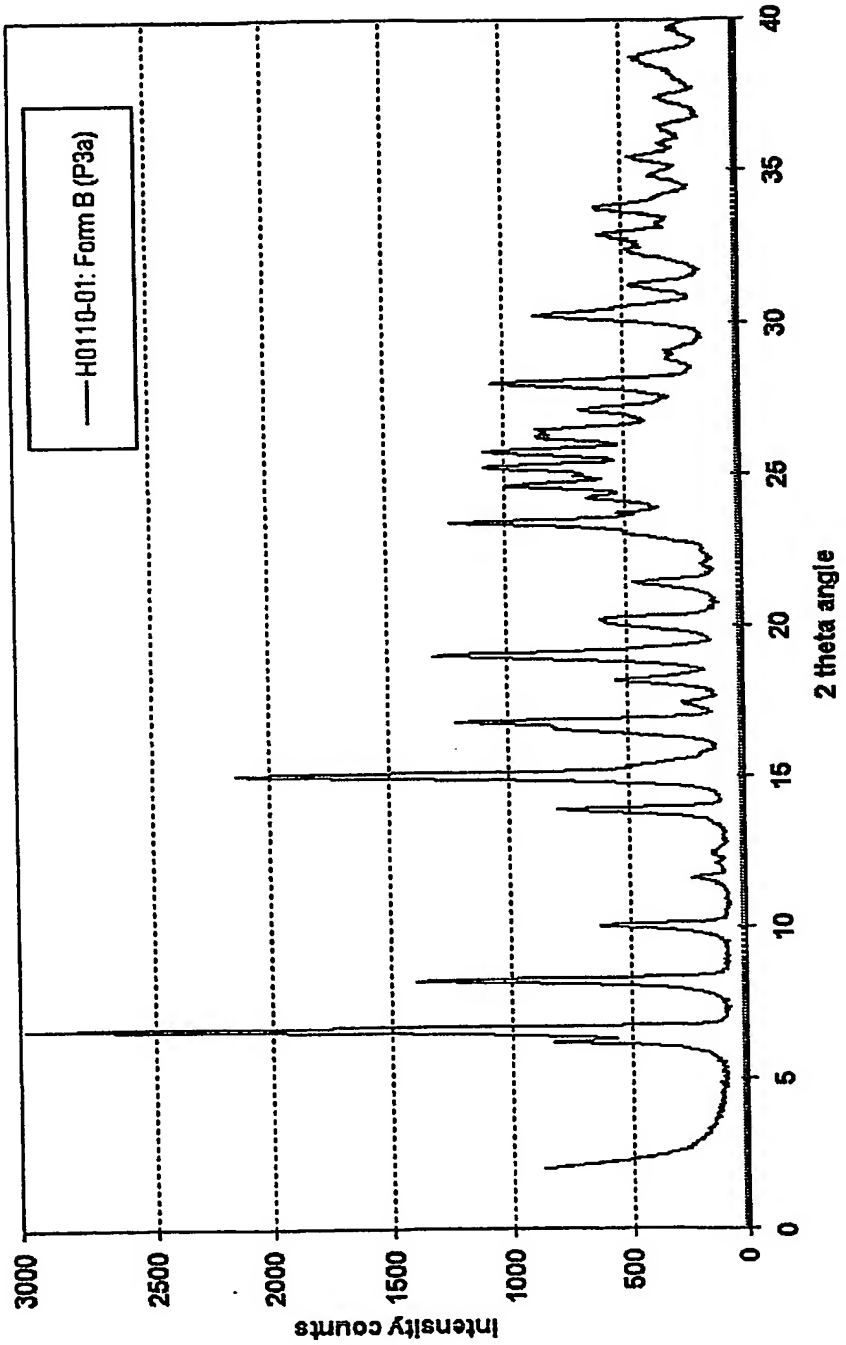
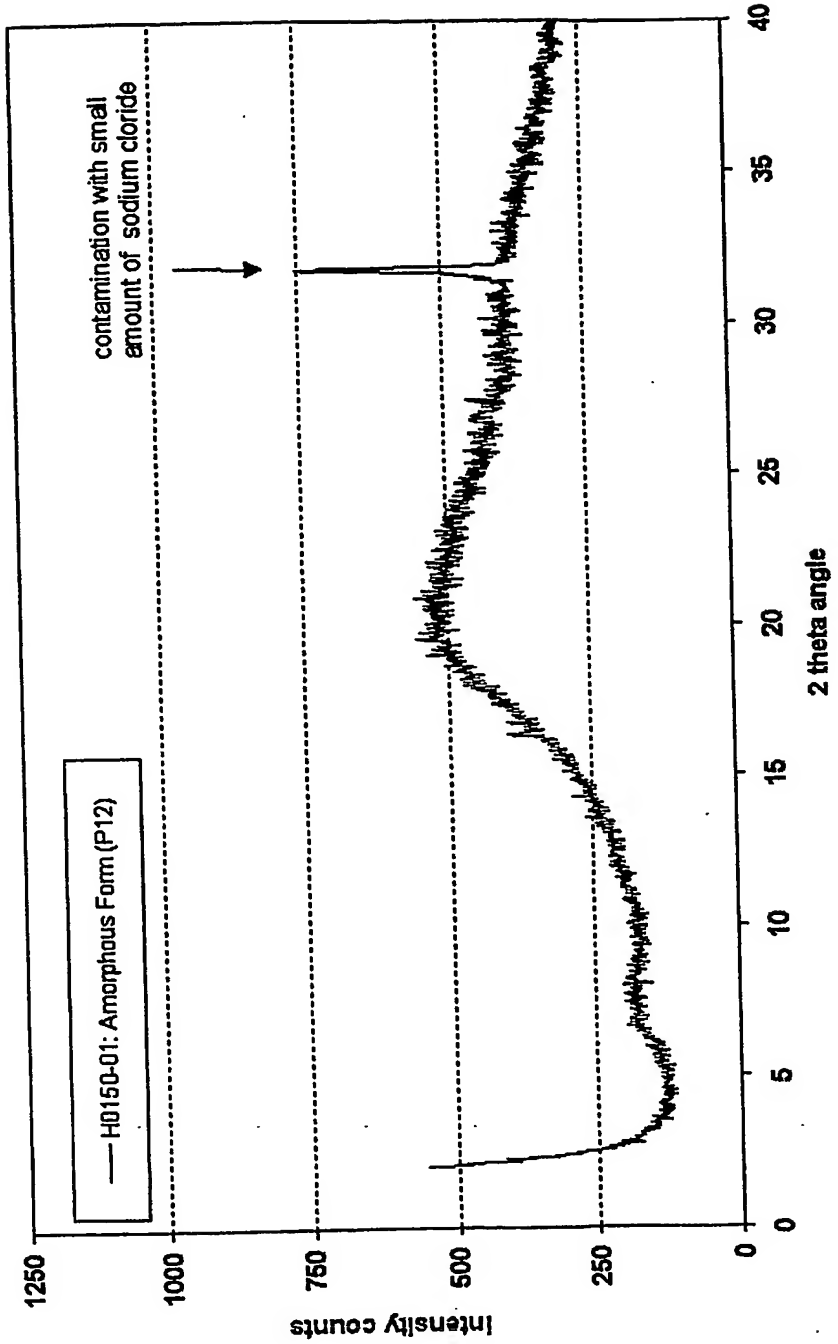

H0110-01: Form B (P3a)
Intensity counts
3000
2500
2000
1500
1000
500
0
2 theta angle
0
5
10
15
20
25
30
35
40

Fig. 4


contamination with small amount of sodium cloride
H0150-01: Amorphous Form (P12)
Intensity counts
2 theta angle
0
250
500
750
1000
1250
0
5
10
15
20
25
30
35
40

INTERNATIONAL SEARCH REPORT

PCT/EP [redacted]7771

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D223/16 A61K31/55

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WATTHEY J W H ET AL: "SYNTHESIS AND BIOLOGICAL PROPERTIES OF (CARBOXYALKYL)AMINO-SUBSTITUTED BICYCLIC LACTAM INHIBITORS OF ANGIOTENSIN CONVERTING ENZYME" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 28, no. 10, 1985, pages 1511-1516, XP000942750 ISSN: 0022-2623 cited in the application example 17 --- -/--	1-25

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 October 2003	17/10/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Von Daacke, A

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP [redacted]/07771

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BEYER S K ET AL: "NOTIZ ZUR SYNTHESE EINES OPTISCH AKTIVES ACE-HEMMERS MIT AMINO-OXO-BENZAZEPIN-1-ALKANSAEURE-STRUKTUR MITTELS ENANTIOKONVERGIERENDER, KRISTALLISATIONSINDUZIERTER RACEMAT-TREMUNG" HELVETICA CHIMICA ACTA, VERLAG HELVETICA CHIMICA ACTA. BASEL, CH, vol. 71, 1988, pages 337-343, XP002207338 ISSN: 0018-019X cited in the application * see compound 3*	1-25
X	US 4 575 503 A (WATTHEY JEFFREY W H) 11 March 1986 (1986-03-11) cited in the application example 12	1-25
X	EP 0 072 352 A (CIBA GEIGY AG) 16 February 1983 (1983-02-16) cited in the application page 109-111; example 27	1-25
A	YU L ET AL: "PHYSICAL CHARACTERIZATION OF POLYMORPHIC DRUGS: AN INTEGRATED CHARACTERIZATION STRATEGY" PHARMACEUTICAL SCIENCE AND TECHNOLOGY TODAY, ELSEVIER TRENDS JOURNALS, CAMBRIDGE,, GB, vol. 1, no. 3, June 1998 (1998-06), pages 118-127, XP000949322 ISSN: 1461-5347 the whole document	1-25

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4575503 A	11-03-1986	US 4473575 A	25-09-1984
		AT 50989 T	15-03-1990
		AT 48598 T	15-12-1989
		AU 574061 B2	30-06-1988
		AU 2443084 A	16-08-1984
		CA 1218993 A1	10-03-1987
		CA 1225397 A1	11-08-1987
		CY 1674 A	10-10-1993
		DD 218359 A5	06-02-1985
		DE 3480705 D1	18-01-1990
		DE 3481612 D1	19-04-1990
		DK 58184 A	11-08-1984
		DK 58284 A	11-08-1984
		EP 0119954 A2	26-09-1984
		EP 0119955 A2	26-09-1984
		ES 8609261 A1	16-12-1986
		ES 8707216 A1	01-10-1987
		ES 8702363 A1	16-03-1987
		ES 8703859 A1	16-05-1987
		ES 8609262 A1	16-12-1986
		ES 8705409 A1	16-07-1987
		ES 8609263 A1	16-12-1986
		ES 8609264 A1	16-12-1986
		ES 8700239 A1	01-01-1987
		ES 8609265 A1	16-12-1986
		FI 840513 A ,B,	11-08-1984
		GR 79809 A1	31-10-1984
		HK 97592 A	11-12-1992
		HU 192394 B	29-06-1987
		IE 56858 B1	01-01-1992
		IL 70881 A	30-10-1987
		JP 1774456 C	14-07-1993
		JP 4060108 B	25-09-1992
		JP 59172473 A	29-09-1984
		JP 1736778 C	26-02-1993
		JP 4021665 B	13-04-1992
		JP 59172475 A	29-09-1984
		KR 9009023 B1	17-12-1990
		NO 840487 A ,B,	13-08-1984
		NZ 207091 A	08-11-1985
		PT 78075 A ,B	01-03-1984
		SG 94992 G	04-12-1992
		ZA 8400958 A	26-09-1984
EP 0072352 A	16-02-1983	AR 240806 A1	28-02-1991
		AR 240807 A1	28-02-1991
		AT 18397 T	15-03-1986
		AU 561395 B2	07-05-1987
		AU 8701482 A	12-05-1983
		CA 1196636 A1	12-11-1985
		CY 1403 A	18-12-1987
		DD 202546 A5	21-09-1983
		DE 3269625 D1	10-04-1986
		DK 358682 A ,B,	12-02-1983
		EP 0072352 A1	16-02-1983
		ES 8502974 A1	01-05-1985
		ES 8601142 A1	16-02-1986
		ES 8606285 A1	01-10-1986

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0072352 A		ES 8504728 A1	16-07-1985
		ES 8604523 A1	01-07-1986
		ES 8602682 A1	16-03-1986
		FI 822770 A ,B,	12-02-1983
		GB 2103614 A ,B	23-02-1983
		GR 77256 A1	11-09-1984
		HK 93387 A	18-12-1987
		HU 189628 B	28-07-1986
		IE 53668 B1	04-01-1989
		IL 66501 A	20-10-1987
		JP 1802522 C	26-11-1993
		JP 5007384 B	28-01-1993
		JP 58038260 A	05-03-1983
		KR 8903425 B1	20-09-1989
		KR 9001190 B1	28-02-1990
		KR 9001191 B1	28-02-1990
		NO 822722 A ,B,	14-02-1983
		NZ 201555 A	11-06-1986
		PT 75395 A ,B	01-09-1982
		ZA 8205779 A	25-04-1984
		US 4410520 A	18-10-1983